

## Review article

# Ten years after the FDA black box warning for antidepressant drugs: a critical narrative review

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## ABSTRACT

**Background:** The United States Food and Drug Administration (FDA) has warned about the increased suicidality risk associated with the use of selective serotonin reuptake inhibitors (SSRI) and venlafaxine in children and adolescents. **Objectives:** To critically appraise the available evidence supporting the FDA Black box warning concerning the use of antidepressants in child and adolescents. **Methods:** A critical review of articles in Medline/PubMed and SciELO databases regarding the FDA Black box warning for antidepressants, and the impact of FDA warnings on antidepressant prescriptions and suicide rates. **Results:** The warning was based on surveys that did not report either cases of suicide nor a significant difference supporting an increased suicidality rate. The concept was defined in an ambiguous way and there is currently more available evidence to support such definition. The use of SSRI and venlafaxine has been associated to lower suicidality rates, but the prescription fall due to the warning increased suicide rates. **Discussion:** Suicidality is an inherent feature of depressive disorders so it would be desirable to consider how much of the phenomenon may be attributed to antidepressants *per se*. It would be appropriate to consider that suicide rates might increase also as a consequence of the warning.

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**Keywords:** Antidepressants, serotonin uptake inhibitors, suicide, United States Food and Drug Administration.

## Introduction

Approximately 2 to 3% of children and 6 to 8% of teenagers suffer from major depressive disorder, considered the main determinant of suicide, and a leading cause of death among teenagers<sup>1</sup>. In fact, depression is present among 46 to 64% of suicidal adolescents<sup>2-4</sup>; an increase of over twenty times the risk of completed suicide<sup>5</sup>. Thus, suicidal conduct is included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders as a diagnostic criterion to the affective disorders<sup>6</sup>.

While a positive correlation exists between the risk of suicide and the severity of affective disorders, subsequent treatment plays a role as a preventive measure. The introduction of new antidepressants (AD), particularly selective serotonin reuptake inhibitors (SSRI) have been a useful mechanism in the rehabilitation of depression, with some countries observing a decrease in suicide rates<sup>7</sup>.

Until the 1980s, depression was primarily treated with AD such as monoamine oxidase inhibitors and tricyclics. Since overdoses of these drugs are potentially lethal, in some cases they were even used as a way to carry out suicidal acts, a situation still worrisome among prescribers, and which opened a discussion surrounding suicidality<sup>8-10</sup>. Nevertheless, the notion that AD precipitate suicide in depressed people was noted by Kielholz and Battagay as early as 1958, relating it to “the rollback phenomenon”, which describes the risk associated with these medications in mobilizing severely depressed patients to attempt suicide as a consequence of psychomotor improvement during the first period of therapy, while still affectively impaired<sup>11</sup>.

The SSRI do not escape from inclusion in the discussion of suicide, on the grounds that Teicher *et al.* reported six cases of patients with suicidal ideas being treated with fluoxetine, highlighting that none had presented such phenomenon previously<sup>12</sup>. That report induced the United States Food and Drug Administration (FDA) to create a panel of experts that gave neither recommendations nor warnings regarding the drug. This despite blind randomized trials

which repudiated a link between previously mentioned AD and increased suicidality<sup>13</sup>. Subsequently, in 2004, the FDA created a new advisory committee that led to one of the most contentious debates linked to suicide: the association between SSRI consumption and the inducement of suicide in children and adolescents<sup>14</sup>. The current FDA warning alludes to an increase in suicidality, a vague concept ranging from mere ideation to the completion of suicide<sup>10-11</sup>, despite the lack of epidemiologic evidence showing a relationship between suicide rates and the prescription of new AD medications<sup>15</sup>.

This intent of this review is to provide a critical viewpoint concerning the FDA warning, its supporting evidence in terms of therapeutic (AD prescription) and epidemiological outcome (suicide rates), the studies that support it, and the research that reinforces the usage of AD.

## Methods

An exhaustive bibliographic search was done through the available articles on the database PubMed, Cochrane Central, SciELO, and on specialized consulting texts, using key words as “suicide”, “adolescence”, “antidepressants” and “FDA”. The date range of the search was from January 1988 through June 2014.

## Results

### Black box warning issued by the FDA

In 2003, the United Kingdom's Department of Health and the FDA issued a public warning against the use of paroxetine in people younger than 18 years old. In August of the same year, Wyeth Laboratories, manufacturer of venlafaxine (dual AD), suggested that physicians should cease prescribing the aforementioned drug in children and adolescents, due to low efficacy and the risk of increasing hostile feelings and suicidal tendencies. Yet in October,

the FDA issued research results involving citalopram, fluoxetine, fluvoxamine, nefazodone, sertraline and venlafaxine, recommending physicians to be cautious in prescribing an AD, with insufficient data supporting the thesis of suicide increase<sup>16</sup>. In December, the British Medicines and Healthcare Products Regulatory Agency suggested that physicians cease prescribing AD for people younger than eighteen (excluding fluoxetine), based on three investigations that cited an apparent increase in suicidal tendencies among children and adolescents<sup>17</sup>. However, the only one of these investigations that were published examined paroxetine versus placebo in the treatment of major depressive disorder, and reported a 3% increase of suicidality for the AD (fourteen out of 378 patients) versus 2.5% for the placebo (seven out of 285 patients), indicating no statistically significant difference<sup>18</sup>. Additionally, the definition of suicidality or suicidal tendencies used was confusing, and included self-harm, suicidal planning and ideation, attempt or completed suicide. Neither of reports stated any death from suicide<sup>18,19</sup>.

The FDA alert, called the Black Box warning, was based on short-term investigations (between four and sixteen weeks) that showed a higher risk of suicidal tendencies (4% on average), the double researched for a placebo, without any accomplished suicides reported<sup>20</sup>. Such action provoked a marked decrease in AD prescription<sup>21</sup>. The American Medical Association and the American Psychiatric Association subsequently warned of the potentially negative consequences that a decline in AD access could have on patients, who might otherwise be significantly benefited by their prescription<sup>22</sup>.

Finally, in October 2004, after assessing a total of 24 studies, the FDA extended the Black Box warning to encompass all AD prescribed to people younger than eighteen. Many of these investigations have not been unveiled to the scientific community, so their methodological rigour could be arguable<sup>23</sup>. In February 2005, the warning was modified by the FDA, stating in a more precise way that the usage of AD would produce an increase in suicidal tendencies and ideations, but not in accomplished suicides<sup>24</sup>. In Table 1<sup>19</sup> suicidal risks for some AD are described, whereas Table 2 shows the results obtained by the FDA when re-analyzing the related events with suicidal acts in young people under AD treatment. For general pathologies the relative risk of suicidal events ascended up to 1.95, without witnessing a statistical superiority with placebo in any case<sup>23</sup>.

**Table 1.** Suicidality rate according to antidepressant versus placebo

Drug	N	Suicidality <sup>a</sup> Antidepressant (%)	Suicidality <sup>a</sup> Placebo (%)	P value
Fluoxetine	458	3.6	3.8	0.9
Sertraline	373	2.7	1.1	0.45
Citalopram	418	8.9	7.3	0.4
Paroxetine	663	3.7	2.5	0.5
Venlafaxine	334	2	0	0.25

<sup>a</sup> Ideation, suicide attempt or self-harm. Modified from Brent y Birmaher<sup>19</sup>.

**Table 2.** Relative risk for suicidal behaviors on clinical trials according to antidepressant

Antidepressant	Major depression studies	All pathologies studies
Citalopram	1.37	1.37
Fluvoxamine	No research	5.52
Paroxetine	2.15	2.65
Fluoxetine	1.53	1.52
Sertraline	2.16	1.48
Venlafaxine XR	8.84	4.97
Mirtazapine	1.58	1.58
Nefazodone	No events	No events
Bupropion	No research	No events
Total	1.66	1.95

Modified Cheung et al.<sup>23</sup>.

In a systematic FDA review, 24 studies were included, of nine SSRI and other AD families, with a total of 4,582 patients with anxiety and affective disorders. Their results showed a relative risk of suicidal behavior and ideation, and self-aggressive behaviors associated with the usage of SSRI in major depressive disorder above 1.66 (CI 95%, 1.02 – 2.68), whereas the relative risk in the total of AD examined for all evaluated pathologies was 0.002 (CI 95%, 0.01 – 0.03). At the same time, the Treatment for Adolescents with Depression Study, a multicenter randomized trial testing the efficacy of AD, reported a statistically significant higher relative risk for SSRI<sup>25</sup>. Also, a systematic review conducted by Hetrick *et al*, which looked at nineteen trials of a range of newer AD compared with placebo, with a total of 3,335 participants showed that those treated with AD had lower depression severity scores and higher rates of response/remission than those on placebo. However, there was evidence of an increased risk (58%) of suicide-related outcomes for those on AD. Nevertheless, the study's trials excluded young people at high risk of suicide and many co-morbid conditions, so participants were likely to be less unwell than those seen in clinical practice. Participants had limited information about the risk of bias, high dropout rates and issues regarding measurement instruments and the clinical usefulness of outcomes, which were often defined differently across trials. The authors concluded that: 1) Due to the methodological limitations of the included trials in terms of internal and external validity, the results must be interpreted with caution; 2) The size and clinical meaningfulness of statistically significant results are uncertain; 3) Fluoxetine might be the medication of choice if a decision to use medication is agreed given the guideline recommendations<sup>26</sup>. On the other hand, an independent meta-analysis, that included 39 studies of AD, did not reveal any significant difference in the ideation or risk of attempted suicide, where one in 147 patients would demonstrate an increased risk<sup>27</sup>. Dubicka *et al*. pointed out similar findings about pediatric depression, examining the suicidal and self-aggressive conduct rates. Total frequency for these events was 4.8% with an AD and 3% with a placebo. When using heterogeneity-sensitive random effects analysis, the relative risk did not encounter statistical significance (RR = 1.58; p = 0.083)<sup>28</sup>.

In May 2012, the American Academy of Child and Adolescent Psychiatry made a public announcement stating that SSRI and other AD would be useful in the treatment of depression<sup>29</sup>, suggesting that therapies with AD continue, but include informing and explaining to the patient's family the existing warning. Moreover, it was advised not to apply such warnings to all children prescribed AD for depression based on: 1) evidence that all AD are efficient in major depression (mainly supported for studies in people above eighteen years old); 2) The study reporting exacerbation of suicidal events does not have sufficient statistical power. Most psychiatrists think that if, in some cases that statement might be true, it is preferable to monitor them rather than to suppress therapy; 3) According to the FDA, only 2% to 3% of children and adolescents increased their suicidal ideations or self-aggressive behaviors after using AD, having no reports of actual suicide; 4) The cost of patients' depression is higher than an increase of 2% in suicidality; 5) At the onset of ideation or suicidal behavior in the beginning of AD treatment, or after a dose adjustment, close surveillance of the patient is recommended during the first month. This is to provide a list of alarm symptoms to be alert to, such as the appearance of or increase in symptoms such as anxiety, panic attacks, psychomotor agitation, akathisia, insomnia, irritability, hostility or aggressiveness, impulsivity, hypomania, and mania. Despite the aforementioned facts, there is no causal link between these symptoms and ideation or suicidal behavior; 6) If the symptoms were severe, had an abrupt start or were not initially present, a change in the therapeutic plan should be considered<sup>30,31</sup>.

Finally, in 2014 the results of a retrospective investigation were published that considered 36,842 children from ages six to eighteen who used fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and venlafaxine, all of which were included in the FDA warning (fluoxetine is the only allowed AD to be prescribed in children and

adolescents by FDA). The research stated that the rates of attempted suicide did not differ significantly among people who received fluoxetine and the other AD not recommended by the FDA<sup>32</sup>.

### Evidence that supports the usage of antidepressants

The individual risk of suicide is multifactorial, but depression stands out as an important factor. Considering that the methodological quality of the research on AD therapy has improved since the warning issued by the FDA, the aspects that support the usage of AD will be described<sup>33</sup>.

### Usage of antidepressants and decrease in suicidal rates

Despite the FDA warnings, there is much AD treatment that results in reducing suicide risks. Thus, in the "Antidepressant Age" (1960-1992) suicide rates associated with affective disorders were reduced from 6.3 per thousand at the beginning of the Twentieth Century to 3.3 per thousand<sup>34,35</sup>. In a study, Kuba *et al.* found that suicidal ideation, self-mutilation and suicide attempts decreased from 47.1% to 22.9% after three months of AD therapy in patients with a mean age of 15.4 years<sup>36</sup>.

The Centers for Disease Control and Prevention indicate that the suicide rate of teenagers increased throughout the 1970's and 1980's<sup>14</sup>, followed by its decrease of 20% to 30%<sup>37</sup> associated with the introduction of SSRI in 1988<sup>38-41</sup>. In fact, between 1985 and 1999, the suicide rate in the US decreased from 12.4 to 10.7 per 100,000, while the prescription of AD (predominantly SSRI) was quadrupled<sup>42</sup>. In North American teenagers, for every 1% increase in AD prescription, there was a decrease of 0.23 suicides per 100,000 annually ( $p < 0.001$ )<sup>43,44</sup>. Additionally, the 13% increase in SSRI sales in 27 countries during 1999 reduced suicide rates by 2.5% in those countries. Particularly in Sweden, suicide fell by 25%, which was likely associated with the 400% increase in AD sales there<sup>45</sup>. Likewise, Bramness *et al.*, through observations made in Norway between 1980 and 2004, found a significant relationship between the rise of non-tricyclic AD sales and the decreased suicide rates<sup>46</sup>. On the other hand, SSRI were introduced in Japan in 1999, increasing its AD prescription by 54%. According to the Japanese Ministry of Health, suicide rates after that year decreased by 6%<sup>47</sup>.

### Elapsed time in antidepressant treatment

Simon *et al.* established a temporal correlation between the usage of AD and suicide rates, reporting that the instances of suicide were significantly lower than the month prior to the beginning of AD treatment. In a total of 65,103 users of AD, the suicide risk during the acute phase of the treatment was one per 3,000, while the suicide attempt was one per 1,000, without a significant association between an increase in these risks and SSRI therapy. Meanwhile, the suicide risk of children and teenagers during the six months following antidepressant indication was 314 per 100,000, this being higher than the month previous to the prescription, showing a decrease immediately after onset of medication and a decline during its usage. While the estimated risk remained relatively stable over the next six months, their confidence intervals were wide, validating the lack to the number of observed events. Researchers assert that a significant increase of suicide risks or serious suicidal attempts existed after initiating SSRI therapy<sup>48</sup>. These findings were confirmed by Simon & Savarino, thus proving the reduction in the suicide rate after AD treatment<sup>49</sup>. Similarly, Jick *et al.* found a strong relationship between suicidal behavior and the time elapsed since the beginning of the AD therapy. Compared to a group that had accomplished ninety or more days of treatment, those who had between one and nine days were four times more likely to commit a non-fatal suicidal act, while those that completed between ten and twenty-nine days were three times more likely, and those who completed reached between 30 and 89 days of treatment only 1.5 times more likely. Moreover, those

who had between one and nine days of treatment were 38 times more likely to commit suicide, those treated between ten and twenty-nine days, were 5.1 times more likely, and finally, those that completed between 30 and 89 days, twice as likely<sup>50</sup>.

### Usage of particular drugs in high risk cases

Mines *et al.* compared a series of clinical parameters and morbidity records in patients assigned to fluoxetine, citalopram and venlafaxine. The venlafaxine patients group was considered to be the most severe due to their psychopathological history with increased suicide risk. Confirming that statement, those treated with fluoxetine and citalopram showed 2.75 times and 2.43 times less suicidal behavior respectively, compared to those who received venlafaxine<sup>51</sup>.

Venlafaxine has been one of the most criticized AD by the FDA. Nevertheless, it has considerable prestige among clinicians for the treatment of severe depression, due in part to its being often prescribed to high-risk groups. Patients assigned to venlafaxine had 6.19 times more risk of being hospitalized for depression compared to patients assigned to fluoxetine, and 4.34 times more than those who received citalopram. Regarding drug history, 27.7% of the group of venlafaxine patients received two or more AD during the last year, while among fluoxetine and citalopram users, 5.5% and 11% respectively, reported such use. Table 3 illustrates the relative risks for general characteristics and behaviors related to suicide for venlafaxine, fluoxetine and citalopram<sup>51</sup>.

### Low plasma levels of antidepressants and discontinuation

Several toxicological studies have revealed that a low proportion of suicide victims had considerable plasmatic levels of AD, indicating that a large number of suicides occurred in people that were depressed and receiving no treatment, failed to adhere to indications, or who had discontinued the medication<sup>52-55</sup>. Relatedly, Isacson *et al.* conducted post-mortem studies of suicides, and did not find plasmatic levels of SSRI in children below fifteen years old, while in the group between fifteen and nineteen years of age, the presence of SSRI was minor compared to other types of AD. This suggests that the hypothesis of suicide being induced by SSRI was not supported by autopsy data<sup>56</sup>, while also concluding that the increase in AD usage in Sweden had been parallel to a significant decrease in suicide rates there.

Meanwhile, Leon *et al.* studied 66 suicides which occurred in New York City between 1993 and 1998, the first six years that paroxetine was available in the United States. Subjects were under eighteen years of age, and chromatographic methods did not find, plasma levels of paroxetine<sup>57</sup>. In other research conducted in New York City which looked at 44 suicides among subjects less than eighteen years old between 1999 and 2002, in only one case (2.8%) was sertraline and bupropion detected during the autopsy, while in all others no presence of any other AD was found<sup>58</sup>. From a sample of 1,635 suicide victims, Marzuk *et al.* showed that 16.4% had a psychotropic prescription, thus reinforcing the above evidence. From the toxicological analysis only 17.9% of deaths by poisoning were found, finding AD in less than half of these victims<sup>59</sup>. So it is supported that the presence of AD in suicidal teenagers is low, contradicting any direct relationship between SSRI usage and child and adolescent suicide<sup>14</sup>. Regarding the discontinuance of AD, Yerevanian *et al.* found that the risk of committing suicide increased five times after suspending AD therapy, claiming that its use would serve as an anti-suicidal protective factor<sup>60</sup>.

### Discussion

"Suicidal tendencies" are central to the FDA's stance against AD prescription, which raises the question: Is suicide an AD side effect or attributable to one of the affective disorders? In lieu of attributing suicidogenic characteristics to AD, we must bear in mind that the regulatory associations do not consider the essential factors

**Table 3.** Risk for behaviors and general characteristics related to suicide according to antidepressant

Characteristics	Venlafaxine N = 27,096	Fluoxetine N = 134,996	Citalopram N = 52,035	Relative risk	
	N (%)	N (%)	N (%)	Venlafaxine versus fluoxetine	Venlafaxine versus citalopram
<b>Previous diagnosis</b>					
Major depressive disorder	20,574 (75.9)	57,918 (42.9)	27,883 (53.6)	4.10	2.8
Bipolar disorder	423 (1.6)	452 (0.3)	328 (0.6)	4.83	2.51
Schizophrenia	705 (2.6)	1,343 (1)	714 (1.4)	2.70	1.91
Anxiety disorder	10,210 (37.7)	28,788 (21.3)	15,560 (29.9)	2.13	1.45
<b>1-year previous event</b>					
Suicidal behaviors	260 (1)	474 (0.4)	207 (0.4)	2.75	2.43
Suicidal behaviors that required hospitalization	99 (0.4)	177 (0.1)	67 (0.1)	2.79	2.84
Hospitalization due to depression	670 (2.5)	551 (0.4)	302 (0.6)	6.19	4.34
Another AD prescribed previously	19,651 (72.5)	37,318 (27.6)	20,563 (39.5)	6.91	4.04
<b>Number of prescribed AD in the last year</b>					
0	7,445 (27.5)	97,678 (72.4)	31,472 (60.5)	0.14	0.25
1	12,132 (44.8)	29,836 (22.1)	14,831 (28.5)	2.86	2.03
2 or more	7,519 (27.7)	7,482 (5.5)	5,732 (11)	6.55	3.1
<b>Current drug usage</b>					
Mood stabilizers	1,010 (3.7)	1,536 (1.1)	977 (1.9)	3.36	2.02
Anxiolytic	2,740 (10.1)	6,893 (5.1)	4,253 (8.2)	2.09	1.26
Antipsychotic	2,653 (9.8)	3,393 (2.5)	2,230 (4.3)	4.21	2.42

Modified from Mines et al.<sup>51</sup>.

that research has demonstrated, such as the severity of depressive symptoms, existence of initial suicide ideation, despair, impulsivity, previous suicide attempts, psychiatric disorder and suicide family records, comorbidities with other psychiatric disorders (e.g. alcohol or drug abuse), medical pathologies linked to pain, treatment adherence, pharmacokinetic parameters (e.g. increased metabolism with lower plasmatic concentrations than the therapeutic ones), and time elapsed since the onset of treatment<sup>61</sup>. Neither the psychosocial factors nor easy access to any suicidal methods are considered. It is questionable to not only attribute suicide to AD *per se* but to the presence and increase of suicidal behaviors, especially since these behaviors are inherent to mood disorders, estimating that between 60% to 70% of depressive people experience suicidal ideation and between 10% to 15% actually commit suicide<sup>62</sup>. At first glance, the fact that significant differences are observed in comparison with placebo may allow one to conclude that AD induce suicidality; nevertheless, those findings can be methodologically questioned, due to the fact that researchers would rarely administer any placebo or AD to groups of patients with similar depressive severity due to ethical constraints, rendering them hardly comparable. An inherent problem with the FDA's systematic review is the retroactive gathering of relevant information, and the lack of a clear definition pertaining to suicide-related events. In this sense, only the Treatment for Adolescents with Depression Study<sup>63</sup> comprehensively evaluated the phenomenon from initial quantities of suicidal ideation and associated behaviors. Suicide varies individually, thus only randomized trials with large sample sizes would have enough statistical significance to demonstrate any difference in the suicide rates linked to AD versus placebo. Nevertheless, with suicide being a low-frequency event, it is difficult to perform a clinical trial large enough to obtain a causal hypothesis. This is a problem that could be solved through meta-analyses of existing randomized clinical trials. However, the period of time clinical trials are usually conducted may be insufficient to establish long-term treatment benefits. Additionally, suicidal behaviors usually constitute exclusion criteria due to their ethical limitations and practical difficulties<sup>46</sup>.

Multiple factors exist which can be linked to the suicidality phenomenon. Firstly, not every AD is effective on any specific patient, nor is the prescribed dosage always sufficient to control the intensity of the symptoms. Another factor is the pharmacological

switch from depression to mania (particularly from dysphoric to irritable mania) in bipolar patients treated with AD in absence of mood stabilizers<sup>64</sup>, leading to self-aggressive behaviors. In terms of treatment temporality, there appears to be an inverted relationship between suicidal behaviors and AD exposure time, raising the question as to what methodology was used in the studies selected by the FDA looking at suicide risk during the first days of therapy compared to the risk in people who do not receive AD. Also, unlike adults with whom psychiatric assistance is often sporadic, in child and adolescent psychiatry the patient is commonly brought to treatment by their parents. As such, professional assistance may be sought once the responsible adult perceives that there may be a serious clinical disorder or it if a suicide attempt has already occurred<sup>65,66</sup>.

The FDA clinical trials do not reflect sustained treatment, since in daily clinical practice the physician may prematurely interrupt the AD therapy due to unwanted adverse effects, to adjust the dosage or make changes to drug combinations<sup>67</sup>. It is precisely this type of practice-based AD treatment that has been successfully applied over the past thirty years in high-risk suicide depressive patients, mainly on an in-patient basis, whose follow up and control may have otherwise been adversely affected due to diverse constraints<sup>11</sup>. Considering that depression is the disorder most-linked to suicide<sup>68-70</sup>, it is reasonable to propose that a close surveillance of the patient could be a protector factor against the phenomenon, specially considering other variables, such as lack of response for SSRI (20% to 30%)<sup>71</sup>, patient non-compliance (15% to 20%)<sup>72</sup> and patients misreport about compliance (even higher in adolescents, particularly if there is no direct supervision). It is for this reason that fluoxetine, with a longer half life than the other SSRI, would not leave a "therapeutic gap" if the drug intake is irregular, which helps explain why fluoxetine has been the least challenged AD by the FDA.

Klein argue that the central concern of the FDA is that AD are potentially lethal, while it is unsupported by research on any case of suicide, instead using the concept of "suicidality" as a substitute for "suicide" and thus overestating the risk. Furthermore, the FDA's findings appear to be based on inferences, since the evidence was obtained in a manner that is not methodologically reliable, nor fulfilling the requirements of the definitions of "suicidal tendencies" utilized by the standardized scales<sup>22</sup>.

## What factors linked to antidepressants could increase suicidality?

Although Khan *et al.*<sup>73</sup> and Gunnell *et al.*<sup>74</sup> concluded that there was not an impact on suicide secondary to the use of AD, there was an increase of self-aggressive behaviors. Some proposed mechanisms to explain the relationship among AD, ideas, and suicidal behaviors<sup>75,76</sup>, are psychomotor stimulation, depression paradoxical deterioration, akathisia, panic attack or anxiety onset, pharmacological switch to mania, induction to obsessive concern with suicide, and aggressive “borderline reactions” or paroxysmal disorders to electroencephalogram that might alter impulse control<sup>61,73-76</sup>. For example, AD with short half-lives may induce, initially, serotonin level fluctuations, which may lead to akathisia, therefore increasing suicidal risk associated with desperation and unrest<sup>77</sup>.

In relation to genetic influence, Menke *et al.* did a genome-wide association study to identify genetic markers linked to emergent suicidal ideation resulting from the AD treatment, finding a very low proportion of genetic factors related to this phenomenon. The results suggest that combinations of some genetic markers could be used to identify patients with this risk<sup>78</sup>. Additionally, an investigation into clinical and genetic predictors of the increase of suicidal ideation by patients undergoing therapy with AD assessed the effects of paroxetine, venlafaxine, and clomipramine. The increase of suicidality was linked to the severity of the affective disorder and the AD treatment when some defined genetic sequences were present, with the exception of paroxetine, which did not show a significant relationship with the aforementioned risk. Some genome sequences were described as stronger guidelines than others in suicidal ideation increase across the therapy, whereas others exhibited a differential association according to the AD type. The FKBP5 gene that codifies proteins linked to glucocorticoid receptor would be associated with the misregulation of the hypothalamic-pituitary-adrenal axis during AD treatment, and the physiopathological mechanism was proposed as responsible for the increase in suicidal ideation. Nevertheless, the authors support the AD prescription in patients displaying suicidal ideation, taking into account the potential benefits of therapy<sup>79</sup>. Pan *et al.* described a crucial element of suicidality, independent of AD prescription, when reporting a new variant of guanosine triphosphate cyclohydrolase deficiency in young men with severe major affective disorder with multiple suicide attempts. This deficiency was linked to some biochemical mediators in the biosynthetic pathways of serotonin and dopamine in cerebral spinal fluid, demonstrating impairment in this metabolic pathway. Through the replacement of these mediators, suicidal ideation was lessened and there was significant improvement in the affective disorder<sup>80</sup>. Although these investigation trends are interesting, it would be overly-reductionist to only consider the biological-molecular aspects involved in the comprehension of suicide, regarding the inherent biopsychosocial nature of this topic.

## Epidemiological effects following FDA warning

Approximately one month after the FDA warning was published, the prescription of AD in the United States had decreased by 10%, and by June 2005 it had decreased an additional 10%<sup>81</sup>. Simultaneously, Hamilton *et al.* noted that after ten years of decrease in the annual suicide rates in North American children and teenagers, an increase of 18% was observed in people between one and nineteen years of age during 2003 and 2004, suggesting that this change may be the result of the FDA recommendation<sup>82</sup>. In a comparative analysis, Gibbons *et al.* found that the usage of SSRI in children and adolescents decreased by 20% in the Netherlands and the United States, proving a correlation with the increase of the 49% and 14% in suicide rates, respectively<sup>83</sup>. Nevertheless, Kurdyak *et al.* stated that the FDA warning was not associated with a significant change in AD prescription in Ontario (Canada) in patients under twenty years old. Meanwhile, the British warning about the prescription of paroxetine in this population

contributed to a significant decline in its prescription by 54% ( $p = 0.03$ ) immediately after the first warning by the *United Kingdom Committee on Safety of Medicines*. The authors argue that the drastic change in paroxetine usage in contrast with AD prescription was due to the British warning being more specific, since it only covered one AD. On the other hand, physicians in Ontario could have prescribed a substitute for paroxetine, while the FDA warning fell on an AD series, thereby leaving professionals without adequate replacement treatment options<sup>84</sup>.

These studies demonstrate a radically diametric effect from the warning issued by the FDA. It is clear that a posterior amplification of the black box warning had an additional impact on practice. In parallel, the FDA recommendation which suggests closer therapeutic contact does not consider the current problems of the mental health system, including low coverage by insurance plans for mental disorders, strict limits on visits to hospitalized and ambulatory patients, restricted access to mental health providers, *inter alia*. Additionally, the current deficit in professionals (child and youth psychiatrists in particular) is not expected to be reversed in the short term, which may be seen as a reason why this tight control becomes difficult<sup>85</sup>.

## Conclusions

Aside from being contradictory to present evidence, assigning a suicidogenic role to AD implies debugging every biological, social and psychological factor that impacts the act of suicide, which itself is a multifactorial phenomenon, and thus not attributable to a single cause. Indeed, many studies that underpin the FDA's stance on AD and suicide risk are still unknown to the scientific world, while others lack a rigorous methodology, or indicate results that do not reach statistical significance. Although the therapeutic effects of SSRI and venlafaxine in young patients may be limited, reasonable evidence does exist which supports its use in the treatment of depression. Based on this, the FDA warning itself might paradoxically be contributing to an increase in suicide rates.

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## Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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